

Repair and regeneration of the nephron

Grant Award Details

Repair and regeneration of the nephron

Grant Type: Research Leadership

Grant Number: LA1-06536

Project Objective: To study in detail the repair and regeneration of the nephron, following kidney injury in the mouse. In year 2, work on human fetal kidney progenitors was started.

Investigator:

Name: Andrew McMahon

Institution: University of Southern California

Type: PI

Disease Focus: Kidney Disease

Human Stem Cell Use: Embryonic Stem Cell

Award Value: \$5,672,206

Status: Active

Progress Reports

Reporting Period: Year 1

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Reporting Period: Year 2

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Reporting Period: Year 3

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Reporting Period: Year 4

Grant Application Details

Application Title: Repair and regeneration of the nephron

Public Abstract: Kidney function is essential for removing the wastes that result from normal cell function and maintaining water and salt balance in our internal tissues. These actions are carried out by roughly a million nephrons within the kidney that filter all the body's blood roughly once every 1-2 hours. The kidney also regulates other tissues controlling blood pressure and blood cell composition, and regulating the strength of bone by activating vitamin D. Chronic kidney injury over time results in a loss of normal kidney function leading to end stage renal disease (ESRD). ESRD affects 500,000 Americans and its prevalence is increasing with a rise in diabetes and hypertension. ESRD is associated with significant morbidity and mortality: ultimately kidney transplant is the only cure but for every four patients requiring a transplant there are only enough available kidneys to help one. Life-threatening kidney injury also occurs through acute damage particularly in hospital settings where infection, toxic drugs or ischemia during surgery kills cells in the nephron shutting down the kidneys. Animal studies indicate that the kidney is unable to make new nephrons: the full complement of nephrons for life are established prior to birth. However, the damaged nephron has a limited capacity to restore activity through the regeneration of missing cells by their surviving neighbors.

Kidney stem cells give rise to all specialist parts of the complex nephron structure during kidney development. New genetic approaches in the mouse have enabled the isolation of these stem cells providing an opportunity to develop strategies to propagate and differentiate kidney stem cells into nephrons in the tissue culture dish. We expect that the insights gained from these studies will facilitate the translation of de novo nephrogenesis to human nephron cultures, and as a result, the development of new approaches to study and treat kidney disease. An alternative approach comes from the observation of limited self-repair by cells within damaged nephrons. The molecular and cellular processes at play in the damage-repair responses are largely unknown but elucidating these mechanisms will facilitate development of novel strategies to either augment the repair process following damage or prevent tubule damage in the first instance within at risk patients. Mouse models again provide a way forward to this long-term goal. By isolating repairing cells, and comparing gene expression signatures amongst damaged, repairing and healthy cells, we will identify repair specific responses and test the ability of candidate repair regulators to enhance the restoration of kidney function.

Statement of Benefit to California: Approximately 1% of Medicare enrollees in the State of California have End Stage Renal Disease and this number will rise. There is no effective cure aside from kidney transplantation, too few donors, and a high morbidity and mortality associated with long-term dialysis. Approximately 5-7% of hospitalized patients experience acute kidney injury, a leading cause of mortality in institutionalized settings. The target of kidney injury and disease is the nephron, all nephrons form during fetal life and self-repair within nephrons is thought to restore normal function. Through identifying conditions that support stem cells capable of new nephrogenesis and generating new nephrons from these cells, we will be able to explore approaches to restoring kidney function that are not currently possible. Further, the identification of factors associated with normal nephron repair will enable functional investigation of their potential clinical significance in kidney injury models. Given the fiscal cost of kidney disease within the State, the toll of kidney disease on patients and their families, and the lack of alternatives – developing approaches that treat disease would have a significant impact.